Physiology of Pregnancy

Introduction

For most of gestation, the placenta is what drives all the changes in mom and governs how the fetus develops. Later in gestation, when there are fetal pituitary and adrenal glands, there is more cross-talk between the fetus and mom, but still, it occurs **through the placenta**. Therefore, for most of gestation, the fetus is functionally passive. Although the cells are actively replicating to form the organs of the eventual neonate, they do so based on what the placenta gives them. Instead, the **placenta drives the changes in mom** and **provides everything from mom to the fetus**. The placenta makes hormones, the placenta takes up every molecule the fetus needs, and the placenta protects the fetal microenvironment. For example, even in a pregnant woman with a testosterone-producing tumor, despite testosterone being a steroid (lipophilic) hormone, no testosterone is detectable in the umbilical cord, the placenta having converted it entirely to estrogen.

This lesson is **about mom** and what pregnancy does to her body. However, because the placenta instructs mom and influences all the changes that happen to her, we must first start by understanding the role of the placenta throughout pregnancy. Firstly, the placenta **steals from mom**. The placenta will take whatever baby needs from the maternal circulation. Some molecules passively pass through the syncytiotrophoblast layer, but almost all molecules that enter the fetal circulation are selected by the syncytiotrophoblast (remember that there are no paracellular spaces and no plasma membranes). Secondly, the placenta **alters the function of every one of mom's organs** through placental hormones.

In the beginning, the placenta (as the outer cell mass of the blastocyst) releases **β-hCG** (human chorionic gonadotropin) to rescue the corpus luteum, sustaining it and its production of **progesterone** for the first 8 weeks of pregnancy. Corpus luteal progesterone silences the HPO axis, preventing any new follicle stimulation or estrogen production from the ovaries and maintaining the endometrium in the secretory phase, thus preventing the endometrium from sloughing off. β-hCG peaks around week 8, then wane. Waning β-HCG causes the corpus luteum to eventually wane as well, and it becomes the corpus albicans. As the β-hCG level decreases, the progesterone from the corpus luteum also decreases. Around week 8, the placenta also starts making **progesterone** and **estrogen** (as in other lessons, multiple forms of estrogen and two forms of progesterone are being produced, but we are going to represent them as one estrogen and one progesterone). Estrogen and progesterone have the best-understood effects on mom's physiology (and in the next lesson we will see how the relative levels of estrogen and progesterone contribute to the changes in mom's uterus in preparation for delivery). But the placenta also makes a few other hormones with their own effects. Specifically, **human chorionic somatotropin** (hCS, also known by its original name, human placental lactogen, hPL), the function of which is uncertain, and **placental growth hormone** (PGH), which facilitates the endocrine growth factors that drive fetal development and alter maternal metabolism to favor getting baby nutrients for storage. The placenta also releases **parathyroid hormone-related peptide** (PTHrP), though in a nonlinear fashion compared to placental growth. This is also the only time this molecule is seen physiologically rather than as part of malignancy-induced hypercalcemia. This entire lesson is about what happens to mom as a result of progesterone, estrogen, PGH, and PTHrP. This is the preview.

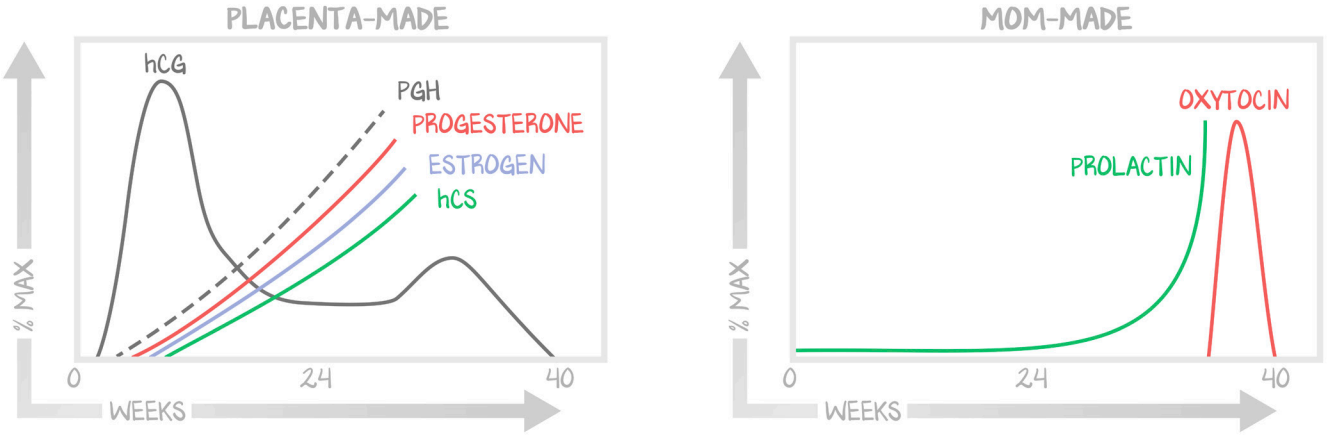

Figure 1.1: Hormones in Pregnancy
The placenta hijacks the maternal endocrine pathways. The placenta is responsible for the production of β-hCG early in the pregnancy, sustaining the corpus luteum. That is the source of progesterone for the first 8 weeks. Around 8 weeks' gestation, the placenta makes the progesterone. The placenta also makes human chorionic somatotropin (hCS; formerly called human placental lactogen [hPL]) and placental growth hormone (PGH) as well as some others. These are the ones we'll focus on in this lesson. The placenta regulates the maternal hormones after the corpus luteum wanes. Maternal prolactin increases toward delivery, and oxytocin spikes to trigger delivery. Prolactin and oxytocin are elevated by breastfeeding—the oxytocin spikes, and the prolactin is sustained.

In addition to the hormones mentioned above, there is a hormone called **relaxin**. It is included at the end of the list and given its own paragraph because it is an often-discussed but poorly understood molecule. Like progesterone, it is released by the corpus luteum. When women with a typical pregnancy (ovulated, had a corpus luteum, produced relaxin) were compared with women who achieved pregnancy through an egg donor (did not ovulate, no corpus luteum, no relaxin), there were no significant differences in the courses of their pregnancies. Relaxin was detected only in the women who had a pregnancy from their own ovulation. This means the complete absence of relaxin resulted in the same pregnancy and the same delivery (with statistically insignificant variations, of course). Relaxin is produced by every mammal, but performs slightly different functions. In rats and horses, relaxin softens the cervix, inhibits uterine contractions, and relaxes the pubic symphysis—changes that are also seen in humans. But in humans, it doesn't seem to be a result of relaxin. The closest medical science has gotten to understanding the function of relaxin in humans is that it might activate matrix metalloproteinases (MMPs) that initiate the rupture of membranes. Relaxin is hypothesized to induce the rupture of the follicle, facilitate implantation, inhibit uterine contractions, and initiate parturition. Its role is not well elucidated enough for us to endorse learning it.

Because the placenta influences all of mom's systems and pathways, we have the opportunity to review every organ system, applying the full range of what you already know (the entirety of the Organ System curriculum). Each section starts with a takeaway. Then, we use the remainder of the section to explain the mechanisms behind the takeaway.

Cardiovascular System 1: MAP, SVR, and PL

Takeaway: Blood pressure falls, blood volume increases, and systemic vascular resistance decreases.

Progesterone acts as a **smooth muscle dilator** in the arterioles. How, exactly, is not known yet; but it does. Despite evidence that progesterone upregulates the expression of the angiotensin 2 (Ang 2) receptor, AT_1, during pregnancy, the systemic vasculature is refractory to the infusion of Ang 2. This refractoriness vanishes quickly (15 minutes) after delivery, but can be sustained with the administration of intramuscular progesterone. This defies what we have taught you about steroid hormones, which

alter gene expression and therefore sustain an effect over hours to days, but it is true nonetheless. Progesterone **blocks the ability of Ang 2 to "tense the angios."** However, it is not an Ang 2 blocker, as it does **not block the ability of Ang 2 to stimulate aldosterone**. Both are relevant to this discussion.

Progesterone initially **decreases the systemic vascular resistance** (SVR) by dilating the arterioles. This has a major effect on the renin-angiotensin-aldosterone system (RAAS). The macula densa of the JG apparatus—the flow sensor in the nephron, the Katrina switch—monitors flow through the nephron. The JG apparatus communicates with the afferent arteriole through local molecules—nitric oxide and adenosine. The JG apparatus communicates with the efferent arteriole through the RAAS by releasing renin and eventually reaching Ang 2. Progesterone blocks the ability of Ang 2 to constrict the efferent arteriole, and thus the efferent arteriole dilates, decreasing the glomerular filtration rate (GFR). The JG apparatus **increases renin release** in response to the falling GFR, thereby driving the RAAS more and more. Ang 2 cannot "tense the angios," but it can stimulate aldosterone. The **aldosterone level rises**; more ENaC channels are inserted into the collecting ducts of the nephrons. More sodium is absorbed, and because sodium = volume = preload, **preload increases**.

Blood volume increases during pregnancy. There are increases in both red blood cells and plasma. We talk about red blood cells later in this lesson. The **increase in plasma volume** is the increased preload. Blood volume can increase as much as 50% in a singleton pregnancy, and up to 100% in a twin pregnancy. The increased plasma volume ensures that there is sufficient perfusion to the placenta and that mom doesn't die during delivery. The normal human cardiac output is 5 liters per minute. A soldier who is hit with a rifle round and loses a liter of blood will die without volume resuscitation. A liter of blood lost during delivery is a normal amount, and mom doesn't even feel it. She'll also experience massive diuresis when she's through, as the placenta's progesterone sustains her cardiovascular system in this high-preload state. After the placenta is gone, so too is the stimulus to sustain the increased blood volume.

Progesterone is responsible for the initial decrease in SVR, but as the pregnancy progresses, **connection to the placenta** continually decreases the SVR. The intervillous spaces are continuous with the maternal circulation. They form the effective capillaries, but they are more cavernous than normal capillaries. The presence of those low-pressure vascular spaces is akin to the inverse of those silly questions we asked you back in the Cardiac module. What happens to the SVR when you clamp the hepatic artery? It increases, because all arterioles are in parallel, and clamping the hepatic artery robs the system of all the distal vessels. What happens to the SVR when you release that clamp? The SVR decreases, because we effectively add all the vessels back to the system. Well, the placenta is like releasing the clamp, adding more vessels. And because the **placenta adds more vessels as it grows**, the SVR progressively decreases. The placenta not only adds more vessels, but it also connects to the spiral arteries by having the cytotrophoblasts invade them, kick the endothelial cells out, and effectively poison the vascular smooth muscle cells to ensure the involved arterioles stay open. So, both the **addition of vessels** and the effective **vasodilation** of maternal vessels decreases the SVR.

The MAP does change. The reduced SVR outpaces the accumulating preload. Thus, the MAP gradually decreases, reaching its nadir between 24 and 26 weeks of gestation. As the changes in SVR taper off and preload catches up, the blood pressure gradually returns toward prepregnant levels as delivery approaches. Because blood volume increases, **preload increases**. With increasing preload, there is **increased stroke volume** and, therefore, **increased cardiac output**. The heart rate does not change much until the third trimester.

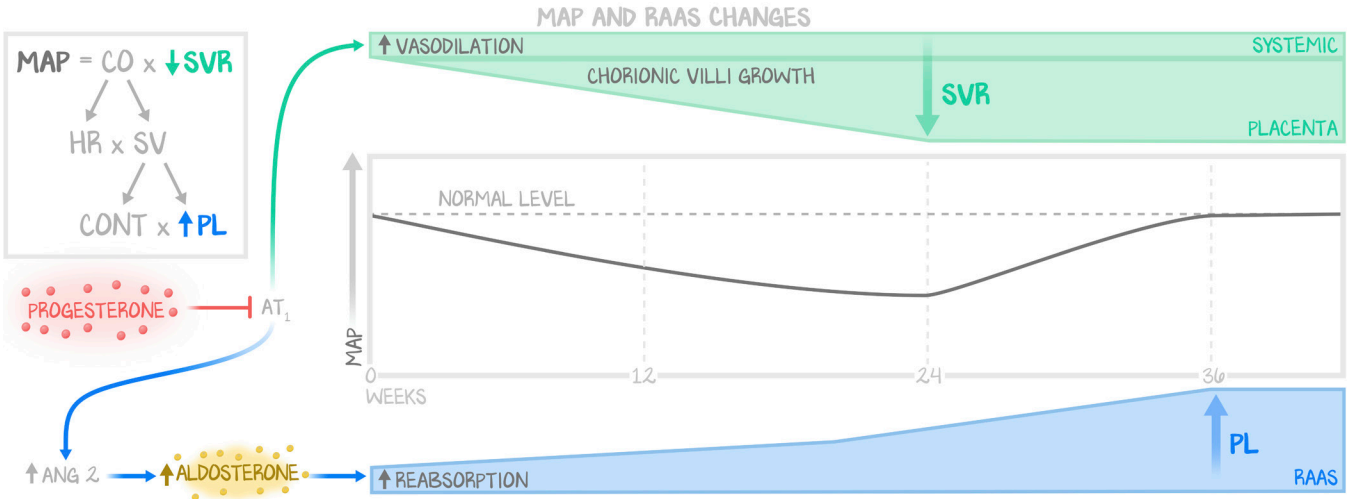

Figure 1.2: MAP and RAAS Changes
The initial change in mean arterial pressure (MAP) comes from progesterone, decreasing the systemic vascular resistance (SVR). The kidnies' response of increasing sodium absorption, thereby holding on to preload, compensates for the change in SVR. But then, for the first two trimesters, the chorion steadily expands, adding more and more villi to the maternal circulation. The trophoblasts poison the vascular smooth muscle cells of the arterioles (leading to vasodilation), and the addition of more and more extravillous spaces equate to the addition of blood vessels in parallel (effectively vasodilation). Thus, there is a progressive reduction in SVR as the chorion continues to grow, and the RAAS responds by increasing reabsorption to re-establish the MAP setpoint. Mom's blood pressure decreases because of the reduced SVR, then nadirs at 24 weeks. Around the start of the third trimester, the chorion is as large as it will be—it stops growing. There is no further reduction in SVR. This enables the RAAS to catch back up. Additional preload restores the balance, leading to extra blood cells and extra blood volume for mom to survive the delivery.

Cardiovascular System 2: Arteries, Veins, and Capillaries

Takeaway: Mom develops edema and nocturia.

All of that extra fluid is something expectant moms tend to notice. Although the production of proteins and red blood cells increases, preload increases more and faster than the proteins and cells that contribute to serum oncotic pressure. Because these blood proteins and cells are diluted by the excess volume, the oncotic pressure is reduced. With the excess volume, there is increased hydrostatic pressure at the capillaries, especially where increased by gravity (e.g., dependent areas, like the feet), and **mom swells**. Edema of the feet, ankles, and even legs is a common complaint of pregnancy. When she lies down (e.g., during sleep), gravity no longer keeps the edema in her legs, and that volume is able to return to the right heart. That increased venous return is increased cardiac output for the left ventricle, and the stretch of the cardiac myocytes better optimizes the sarcomere length, leading to higher perfusion pressure. Increased perfusion to the kidneys, which then filter the added volume into her bladder, results in **nocturia** (waking up to void), another common complaint of pregnant women.

There is a consequence of the growing uterus that contains the growing fetus. The increased preload protects against not only hemorrhage during delivery but against compression of the inferior vena cava by the gravid uterus, especially while lying flat on her back. A heavy uterus can act as a tension pneumothorax does on the vena cava—compressing it, preventing venous return, and causing hypotension. A heavy uterus can also compromise blood flow to the uterus by compressing the arteries from the aorta, leading to fetal distress. In either circumstance, turn mom on her left side (if a provider is taking action because mom cannot) or have her kneel on her hands and knees (if mom is taking action) to use gravity to alleviate the compression.

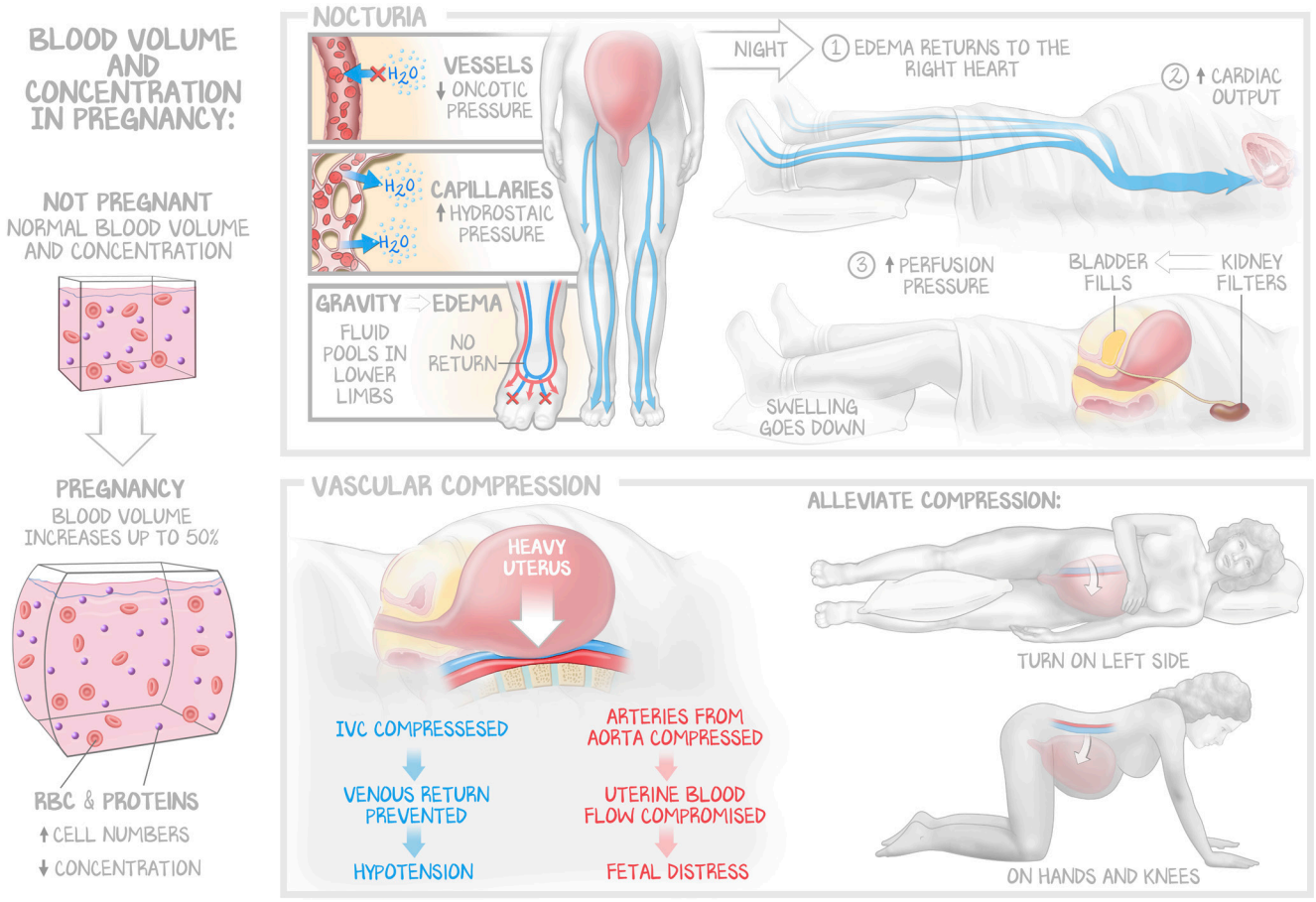

Figure 1.3: Edema, Nocturia, and Hypotension

Hematological Changes

Takeaway: Hemoglobin decreases despite increase in red blood cell count. Pregnancy is a hypercoagulable state. Mom should take folate and iron supplements to sustain her own and baby's hematopoietic needs and cellular division.

Mom **makes red blood cells**. Mom makes red blood cells for the same reason the blood volume increases—to survive delivery and tolerate lots of blood loss. The oxygen-carrying capacity of mom's blood is highest in the third trimester, but that is when she has the **lowest concentration of erythrocytes**. This usually frustrates learners, but we've already taught you that hemoglobin is a concentration, so this should come as no surprise. Because blood plasma volume expands more than the red blood cells, the red blood cell concentration decreases. But both are expanded, so there are more of them than in prepregnancy. Just like the blood pressure, mom's **hemoglobin should decrease**. It should reach a nadir at the same point as the blood pressure, around the start of the third trimester. But it should not fall too far—falling too quickly or dipping below a hemoglobin level of 10 mg/dL, is a sign that something is wrong. OB/GYNs tend to be "crit people," preferring the hematocrit to the hemoglobin. Remember that hemoglobin and hematocrit are essentially the same thing; the hematocrit is approximated by three times the hemoglobin.

Mom makes red blood cells, but **baby also makes red blood cells**. The production of red blood cells (as well as of all of baby's cells) requires **iron** and **folate**. The amount of iron required is staggering,

up to 7 mg/day. Normal iron absorption is typically 1 mg/day. In hemochromatosis (a pathology of iron excess), symptoms are seen when total body iron stores reach 20 g, a level a woman without hemochromatosis would never reach. Pregnancy lasts 280 days. At 7 mg/day, that would be 19.6 g of iron. Of course, that isn't the everyday demand, but the point is that the demand is high, and most women do not have the iron stores to accommodate the placenta's demands/fetus's needs in addition to their own. By the third trimester, over 25% of pregnant women are iron deficient, and multiparous women typically do not adequately resupply their iron stores between pregnancies. This is why daily **prenatal supplements containing 27–30 mg of iron** are recommended for every pregnancy. Folate stores are small, and there isn't anything special to review about folate from mom's perspective (it's much more important for fetal development), but it is just as important to give mom **supplementation with 400 mcg of folic acid** throughout pregnancy. All prenatal vitamins (and many multivitamins) contain this amount. (See Nutrition: Food as Medicine #16: *OBGYN: Pregnancy* for a deeper dive into supplementation during pregnancy.)

It isn't just feeding mom more iron that helps her accommodate baby's needs. Because normal absorption is a mere 10% of what is ingested, it wouldn't be enough just to give her oral iron. But the placenta is sneaky. Even if there is an iron shortage in mom, baby is getting whatever iron mom ingests before mom. There have been cases in which mom had a hemoglobin level of 3 mg/dL and baby's was 16 mg/dL. And if mom is ingesting iron, baby is getting that iron, too. The placenta accomplishes this through **ferroportin**. Remember ferroportin from Heme/Onc? The basolateral domain iron transporter on enterocytes, how iron gets out of enterocytes and into the blood? The syncytiotrophoblast of the placenta has it, too. Only, the **placenta takes iron out of mom's blood** and transfers it to baby's. Both placental and enterocyte ferroportin are under the same regulation: hepcidin. **Estrogen** from the placenta alters gene transcription in hepatocytes to **suppress hepcidin transcription**, thereby tanking hepcidin levels and disinhibiting ferroportin—both the one that brings iron into mom's blood, and the placental ferroportin that takes iron from mom's blood and gives it to baby.

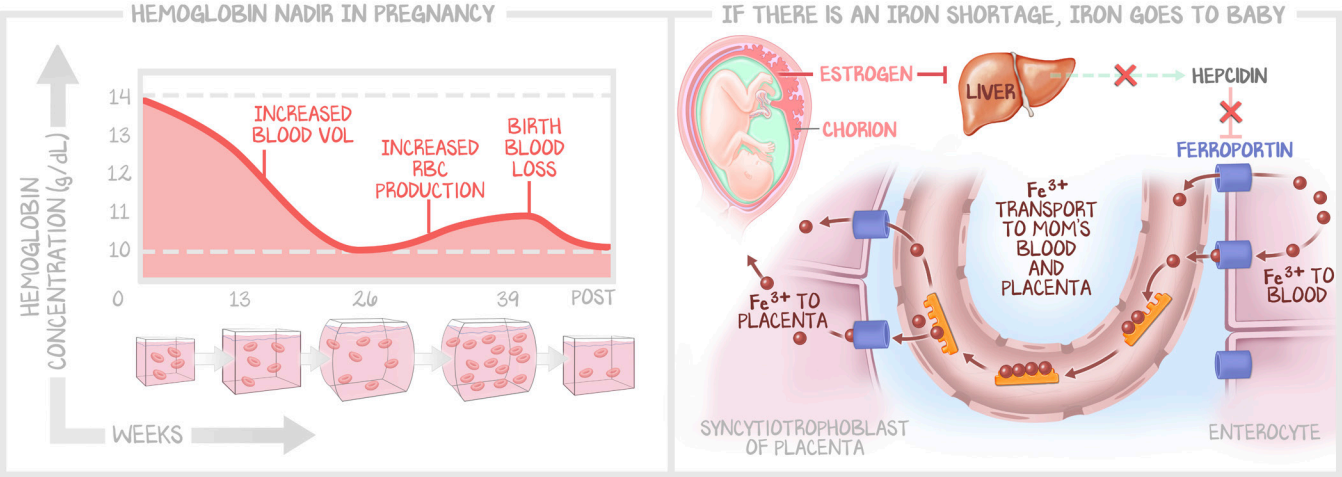

Figure 1.4: Hemoglobin Nadir and Ferroportin Regulation
Maternal hemoglobin decreases for the first two trimesters as the collecting duct reabsorbs more volume than the marrow can keep up with in terms of RBC production. Both blood volume and red blood cell count increase, but the volume increases more/faster than the production of red blood cells. Despite more red blood cells, the blood is relatively dilute. As the chorion stops growing (no further reduction in SVR), the RAAS slows down the reabsorption of volume, but the production of hemoglobin does not stop. Thus, there is a nadir of the hemoglobin level around the start of the third trimester, then a general trend toward normal. At the time of delivery, blood is lost. Just after delivery, there is substantial diuresis, and hemoglobin may normalize or drop slightly lower than the prepregnancy baseline. The placenta enables maternal and fetal red blood cell production by inhibiting hepcidin production and expressing ferroportin—the same enzyme that maternal enterocytes use to absorb iron from the gut, the placenta uses to funnel iron into baby and away from mom.

Pregnancy and the postpartum period are considered **hypercoagulable states**. Estrogen causes the liver to **upregulate transcription** of **clotting factors 7–10** and **downregulate transcription** of the anticlotting **protein C** and **protein S**. Estrogen also increases transcription of endothelial cell components, such as fibrinogen (but also plasminogen), although the **PT and PTT are normal**. Pregnant women have a five- to sixfold higher risk of thromboembolic disease than nonpregnant women.

Anterior Pituitary Changes

Takeaway: Lactotrope hyperplasia and hypertrophy lead to increased prolactin.

To simplify things, we told a white lie in the lesson on the normal breast. In truth, dopamine does inhibit the lactotropes, and progesterone does stimulate the production of dopamine that would inhibit the lactotropes, but **prolactin rises throughout pregnancy**. It is what causes the production of colostrum. **Progesterone** opposes prolactin's effect on gene transcription in the acinar cells of the mammary gland, holding them from active milk production despite prolactin's high concentration in mom's serum.

Despite dopamine's inhibition of the lactotropes, **estrogen's effects on gene transcription** overwrite the dopamine signal. So much so that the size of the pituitary **more than doubles** as estrogen drives both the hyperplasia and hypertrophy of lactotropes. With the increasing size and number of the lactotropes, there is a concurrent rise in prolactin. This increase in cellularity is **not met with concurrent angiogenesis**, rendering the anterior pituitary particularly vulnerable to hypotension. We explored this phenomenon in the Endocrine module—hypotension due to a difficult delivery or complicated by blood loss can lead to Sheehan's syndrome, a means of acquiring panhypopituitarism. We also explained that the ability to lactate is the first thing lost, and other functions may be spared. This is why: the lactotropes are the most vulnerable in Sheehan's because there are more of them, and so many are required to produce the prolactin needed for breastfeeding, yet there is no compensatory increase in their blood supply.

Posterior Pituitary Changes

Takeaway: The left-shifting of ADH thresholds results in decreasing serum osmolarity.

This happens. It is normal for it to happen. But how it happens is not well elucidated. Antidiuretic hormone (ADH), the hormone that inserts aquaporin channels into the collecting duct to reabsorb water, is released from the hypothalamus-as-the-posterior-pituitary in response to either decreasing plasma volume or increasing serum osmolarity. The usual setpoint is around 280 mOsm in the serum. During pregnancy, the serum osmolarity **drifts downward** and should stay above 260 mOsm. The ADH-secretion setpoint drifts with it. ADH also makes mom thirsty, so she drinks water, which is then reabsorbed in the collecting duct. This was why it is so important for you to associate aldosterone with volume and ADH with osmolarity. The sodium level on blood chemistry is not a marker of sodium, aldosterone, or volume; it is a marker of osmolarity. **Low sodium is normal in pregnancy**, and **the later in pregnancy, the lower it can be**.

Insulin Resistance

Takeaway: Placental growth hormone and human chorionic somatotropin impair metabolic tissues' (e.g., adipose and skeletal muscle) ability to take up glucose, resulting in hyperglycemia and hyperinsulinemia. These hormones also increase free fatty acids and ketosis, utilizing ketones to store energy, especially in the third trimester.

Placental growth hormone works just like the growth hormone from mom's pituitary, but it is **released continuously**. The target remains the liver and hepatocytes' expression of insulinlike growth factor 1 (IGF-1). IGF-1 (the growth signal) and thyroid hormone (the spark to ignite all cells) inform baby to grow. So does **insulin**. Because the fetus is passive, if a pregnant woman has poorly controlled diabetes, then her high blood glucose and insulin levels end up in baby, resulting in macrosomia (big baby). But that isn't what happens to most moms.

Every expectant mother experiences **fasting hypoglycemia**, **postprandial hyperglycemia**, and **hyperinsulinemia**. That translates to "the placenta steals glucose from mom (hypoglycemia) and makes sure she has enough glucose around long enough for the placenta to steal it (postprandial hyperglycemia), and mom's pancreas works as expected when there are elevated blood sugar levels (hyperinsulinemia)." Both PGH and hCS antagonize the effect of insulin in metabolic tissues, but it is **definitely not via inhibition of GLUT4 translocation** (the obvious first candidate—if there is no GLUT4 translocation, then no glucose can move). Instead, PGH and hCS compete with cytoplasmic second messengers. The mechanism is fairly well elucidated, but too complex to warrant attempting to explain in this lesson, which is supposed to be a review. In addition, PGH induces **lipolysis** in adipocytes (again a physiological antagonist against insulin's function), liberating fatty acids for the liver to turn into ketones. The placenta passes the glucose and ketones to baby, who uses them for fuel in early gestation and stores them as glycogen and fat in the third trimester, preparing for the metabolic demands of extrauterine life after delivery.

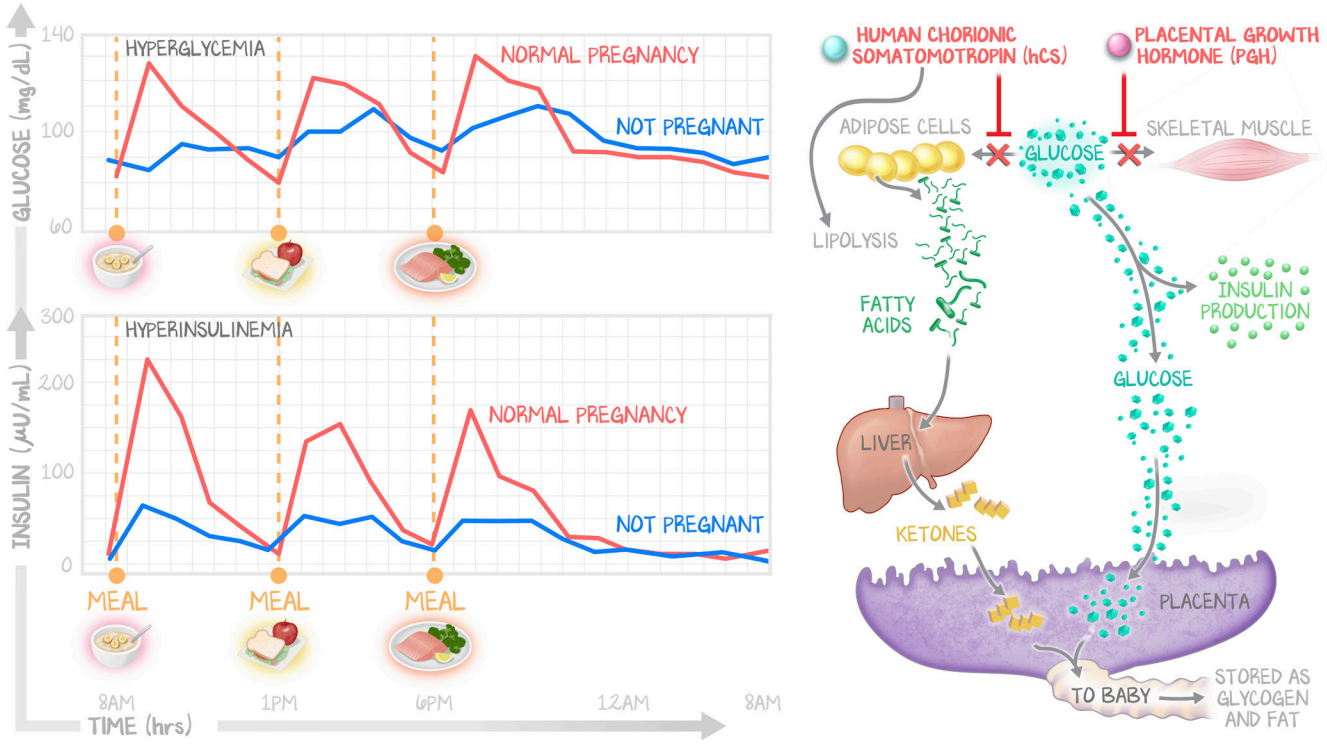

Figure 1.5: Diabetogenic Effects of PGH and hCS
During pregnancy, preprandial glucose levels decrease as insulin does its job (shifting glucose into maternal cells), and the chorion continues to take glucose from the maternal blood. Postprandial glucose levels are elevated as hCS and PGH prevent the uptake of glucose into the cells of metabolism. Postprandial insulin is elevated as a functioning pancreas does what it is supposed to do in a state of hyperglycemia, unaware of the placenta and its diabetogenic hormones.

If mom already has insulin resistance (type 2 diabetes), then the additive effect can provoke **gestational diabetes**. Gestational diabetes is defined as the onset of diabetes **after gestational week 20**. All mothers are induced to hyperglycemia and insulin resistance by the placenta. Mothers with baseline insulin resistance (but don't know that because they don't have hyperglycemia when nonpregnant) find out about that insulin resistance when stressed by the placenta. It isn't the need for gestational diabetes treatment that puts her at risk for developing actual diabetes. It is the fact that she had pre-existing insulin resistance and was on her way to diabetes anyway that provoked the need for treatment for gestational diabetes. Some patients think it is something you catch, then can't get rid of.

Urinary Changes

Takeaway: The GFR increases, the reabsorption of glucose and protein decreases, and the urinary system enlarges.

Initially, the progesterone-prohibiting effects on the efferent arteriole prevented the correction of the GFR by Ang 2, prompting the RAAS to expand the plasma volume. But that effect is present at the start, and doesn't increase with rising progesterone. The SVR continues to fall as more and more placenta adds more and more intervillous spaces and ensures that the spiral arteries remain fully open, their arterioles maximally dilated. The continually decreasing SVR is met with ever-increasing preload, reabsorption of salt and water from the collecting ducts. Preload contributes to stroke volume, and stroke volume contributes to cardiac output. The increased cardiac output causes increased delivery to the glomerular capillaries and an **increased GFR** (50% by the early second trimester). Clinically, this is important when interpreting renal function tests. In pregnancy, the mean serum creatinine level is 0.5 mg/dL, and a creatinine level of ≥ 0.9 mg/dL is considered abnormally high. Similarly, the mean blood urea nitrogen (BUN) level in pregnancy is 9 mg/dL by the end of the third trimester. **A normal creatinine value in the nonpregnant state is too high in the pregnant state.**

The increased GFR also affects urinalysis results. **Glucosuria** and **proteinuria** may not be abnormal in pregnancy, whereas either is a sign of pathology in a nonpregnant person (female or male). The hyperglycemia induced by the placenta, increased GFR, and impaired glucose reabsorption in the proximal convoluted tubules (the mechanism of which is poorly elucidated) result in glucosuria in **one in six normal pregnancies**. But because the deleterious effects of gestational diabetes are so severe, **1-hour** and **3-hour glucose tolerance tests** are performed to rule out gestational diabetes whenever glucosuria is found. Proteins are not supposed to be able to get into the urinary filtrate, having been blocked by the nephrin-bridge filtration slits between podocyte foot processes. But under such high pressure (the elevated GFR), some proteins do get through. Until **300 mg/24 hr**, there is no cause for alarm. The degree of proteinuria increases with advancing gestation, and 300 mg/24 hr is the cutoff for preeclampsia, a systemic disorder caused by vasoconstriction. We have not included it in the Basic Sciences because its mechanism is poorly understood, but it and its related syndromes (eclampsia, which is seizure; and HELLP syndrome, which is hemolysis, liver dysfunction, and thrombocytopenia) are very important considerations in Clinical Sciences. Dipstick analysis, which involves dipping a stick into a urine sample and analyzing the color changes, is easy but inaccurate. A 24-hour urine collection is tedious for the patient, but it is the gold standard. A **spot protein-to-creatinine ratio** can be performed (by the lab) on a urine sample, and approximates the 24-hour urine protein. This is typically the test of choice.

Another urinary system change is the dilation of the ureters. **Progesterone** causes smooth muscle relaxation, which leads to ureteral dilation. Additionally, the growing uterus compresses the ureters, exacerbating proximal dilation. This mechanical compression is greater on the right side than on the left, due in part to the tilt of the uterus (referred to as "dextrorotation" of the uterus) due to its being lifted and rotated by the sigmoid colon on the left. The dilation **is normal**, and **hydronephrosis** and **hydroureter** should not be considered abnormal. However, because the fluid is more prone to

stagnation, the incidence of **pyelonephritis** is higher in pregnant women than in nonpregnant women. Pyelonephritis is associated with adverse pregnancy outcomes, including preterm delivery and low birth weight. Therefore, we screen all women for bacteriuria in pregnancy and treat even asymptomatic bacteriuria with antibiotics to prevent the development of pyelonephritis. Symptomatic cystitis should also be promptly treated, and follow-up cultures should be obtained to ensure complete resolution.

Gastrointestinal Changes

Acid reflux is a common complaint in pregnancy. **Progesterone** is a smooth muscle dilator, so it affects the smooth muscle of the lower esophageal sphincter. This happens early in pregnancy. Furthermore, as the gravid uterus grows it exerts pressure on and compresses the stomach, exacerbating symptoms. Patients experiencing GERD in pregnancy are counseled regarding lifestyle changes, including dietary modifications and elevation of the shoulders and head while lying down. If symptoms persist, calcium carbonate antacids and sucralfate are indicated. Proton pump inhibitors or H_2 receptor blockers are prescribed if the previous measures are unsuccessful.

Another complication of progesterone-mediated smooth muscle relaxation is **impaired gallbladder contraction**. This results in stasis and an increase in bile cholesterol saturation and is thought to contribute to the increased incidence of cholelithiasis in multiparous women. Gallstones can present during pregnancy. The best time for cholecystectomy in pregnancy, if needed, is in the second trimester (this is true of all elective surgeries). The second trimester is far enough along for the gestation to be less sensitive to anesthesia or temporary metabolic derangements, but not far enough along that the uterus is in the way. Not only is it annoying for the surgeon to have a huge uterus in the field, but the gestation is sensitive to external insult, potentially initiating preterm labor.

Finally, progesterone can lead to slow transport times, resulting in **constipation**.

The Effects of β-hCG

hCG sustains the corpus luteum, thereby sustaining the progesterone signal that silences the axis and sustains the endometrium. But it can also cause some unwanted side effects.

Probably the most recognizable symptom (especially for those who have not been pregnant themselves) is **morning sickness**. It is unknown how hCG induces nausea and vomiting, but the fact that it does has been romanticized time and time again in the entertainment industry, so almost everyone knows about morning sickness. Although morning sickness is a nuisance, it isn't dangerous. Until it is. If the hCG level gets very high, often due to an extra-hCG-producing pathology (molar pregnancy or multiple gestations), nausea and vomiting can be so bad as to cause **volume depletion** and **starvation ketosis**, a condition called **hyperemesis gravidarum**. This warrants admission, fluid replacement, antiemetics, food, and a search for a pathologic cause of severely elevated hCG.

Because the luteinizing hormone (LH) receptors are hCG receptors, hCG from the placenta keeps the corpus luteum alive. When the LH surge hits, any follicle that is close to ovulating, but not close enough, is induced to become a corpus atreticum. But what about all those follicles that are not close enough to be killed off? You know, those that will approach readiness to ovulate on the next cycle? The ones least dependent on follicle-stimulating hormone (FSH) as the source of their growth and maturation because they are dependent on LH from the anterior pituitary? Oh, or hCG from the placenta since they have the same receptor. At pathologic levels (and in some normal pregnancies), if the hCG is very elevated, it can stimulate those follicles to grow, forming **theca-lutein cysts**, like the ones we saw in the ovarian cancer lesson.

Because the α subunit of hCG is the same as TSH and the β subunit unit is unique but very similar, hCG has an affinity for the TSH receptor. This is useful (baby needs thyroid hormone and IGF-1 to grow), but not necessarily intended. If there are multiple gestations or a molar pregnancy, the hCG level can get too high. This could provoke overstimulation of the TSH receptor, and mom could experience hyperthyroid symptoms. In some pathologic cases, pregnancy has provoked a thyroid storm. That's a rare occurrence, but still something to know about. Most of the time, it causes the TSH level to fall, presenting as subclinical hyperthyroidism (low TSH but normal thyroid function). The most important thing regarding pregnancy-related thyroid issues has nothing to do with β-hCG, but rather the **estrogen-induced increase** in hepatic proteins, especially **thyroid-binding globulin**. The free thyroid hormone level is normal, but there is more thyroid-binding globulin and, therefore, more total thyroid hormone. **Unless the source of thyroid hormone is levothyroxine** because she has hypothyroidism. Levothyroxine dosing must increase to match the increased thyroid-binding globulin, otherwise there will be more thyroid hormone bound, but less free thyroid hormone.

Weight and Caloric Changes

The subject regarding weight gain and caloric changes is important to the Clinical Sciences, and there aren't any mechanisms to discuss. However, we want to close with a few practical elements regarding metabolism in obstetric care. **Mom is not eating for two.** For more detail on prenatal nutrition and exercise, including special considerations for twin pregnancies, see Nutrition: Food as Medicine #16: *OBGYN: Pregnancy*.

Metabolic rate increases during pregnancy to keep pace with the metabolic needs of the growing fetus and placenta. However, the World Health Organization dispelled the "eating for two" myth with an analysis of the additional energy demands on pregnant women in 2004. General recommendations are not to increase caloric intake during the first trimester and to increase intake by 340 kcal/day in the second trimester and 452 kcal/day in the third trimester. The optimal amount of weight gain in pregnancy depends on the patient's prepregnancy BMI, and it is important to tailor prenatal patient counseling accordingly. Likewise, the amino acid demands increase across the duration of pregnancy, greatest in the third trimester—1 g/kg/day of protein is recommended early in pregnancy, and up to 2 g/kg/day in the third trimester. Eating too many calories merely increases maternal adiposity, weight that mom will need to expend energy to lose after pregnancy.

PREPREGNANCY CATEGORY	BMI	PREGNANCY TOTAL WEIGHT GAIN (LB)
Underweight	< 18.5	28–40
Normal weight	18.5–24.9	25–35
Overweight	25.0–29.9	15–25
Obese	≥ 30.0	11–20

Table 1.1: Pregnancy Weight Gain Recommendations
Recommended gestational weight gain ranges are based on prepregnancy BMI category. Adolescents should be assessed using adult BMI categories. Two-thirds of women gain too much or too little weight during pregnancy.

PREPREGNANCY BMI CATEGORY	1ST TRIMESTER (TOTAL GAIN IN LB)	2ND AND 3RD TRIMESTERS (LB/WEEK)
Underweight	1.1–4.4	1.0
Normal weight		1.0
Overweight		0.6
Obese		0.5

Table 1.2: Recommended Rate of Maternal Weight Gain
Many women gain too much weight during the first trimester. This could be due to a change in eating behaviors or a reduction in physical activity when first-trimester fatigue occurs. The ranges in this table are approximations.

In a low-risk pregnancy, **moderate-intensity exercise** benefits a woman's health without adversely affecting birth outcomes. Guidelines are based on the woman's prepregnancy activity level but are essentially the same as those for nonpregnant women. Previously inactive women should start slowly (e.g., walking) and increase their activity level gradually. Women who were previously highly active may not need to reduce the intensity of their exercise. It is very common for physical activity to decrease late in pregnancy as it becomes progressively more challenging with the extra weight, a uterus in the way, and fluid accumulation. There are no adverse outcomes related to exercise as long as mom ingests enough calories and gains the appropriate amount of weight.

Contraindications for exercise include hypertension, intrauterine growth retardation, cervical incompetence or insufficiency, and persistent bleeding in the second or third trimesters. Contact sports or activities with risk of abdominal trauma or falls (e.g., downhill skiing, soccer, horseback riding) should be avoided.

PTHrP released by the placenta will initially cause the maternal PTH level to decrease. Calcium and phosphorous metabolism are altered, but usually not severely. Eating a regular diet is enough to satisfy the needs of both baby and mom. However, very low calcium intake during pregnancy is associated with preeclampsia. For women who do not consume dairy or calcium-fortified foods, calcium and vitamin D supplements may be needed. Because the placenta drives calcium metabolism, mom takes a compensatory step back, and thus pregnancy is not typically a demineralizing condition. PTHrP does what PTH normally does—accelerates **1,25-dihydroxyvitamin D** production in the kidneys, reabsorbs mineralized bone, retains calcium, and wastes phosphate in the tubules.